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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Part 862

[Docket Nos. 01 P-01 19 and 01 P–0235]

Clinical Chemistry and Clinical Toxicology Devices; Reclassification of Cyclosporine and Tacrolimus Assays'

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to reclassify cyclosporine and tacrolimus assays from class III (premarket approval) to class II (special controls). Cyclosporine and tacrolimus assays are intended for the quantitative determination of cyclosporine and tacrolimus concentrations and are used as an aid in the management of transplant patients receiving these drugs. FDA is proposing this action after reviewing reclassification petitions submitted by Dade Behring, Inc., and Microgenics, Inc. The agency is taking this action under the Federal Food, Drug, and Cosmetic Act (the act), as amended by the Medical Device Amendmentsof 1976 (the 1976 amendments), the Safe Medical Devices Act of 1990 (the SMDA), and the Food and Drug Administration Modernization Act of 1997 (FDAMA). Elsewhere in this issue of the Federal Register, FDA is announcing the availability of a class II special controls draft guidance entitled "Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Draft Guidance for Industry and FDA."

DATES: Submit written or electronic comments by *[insert date 60 days after date of publication in the* **Federal Register].** See section XI of this document for the proposed effective date of a final rule based on this document.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to http://www.fda.gov/dockets/ecomments.

FOR FURTHER INFORMATION CONTACT:' Jean M. Cooper, Center for Devices and Radiological Health (HFZ–440), Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850, 301-594-1243.

SUPPLEMENTARY INFORMATION:

I. Background (Regulatory Authorities)

The act, as amended by the 1976 amendments (Public Law 94–295), the SMDA (Public Law 101–629), and FDAMA (Public Law 105-l 15), established a comprehensive system for the regulation of medical devices intended for human use. Section 513 of the act (21 U.S.C. 360c) established three categories (classes) of devices, depending on the regulatory controls needed to provide reasonable assurance of their safety and effectiveness. The three categories of devices are class I (general controls), class II (special controls), and class III (premarket approval).

Under section 5 13 of the act; devices that were in commercial distribution before May 28, 1976 (the date of enactment of the 1976 amendments), generally referred to as preamendments devices, are classified after FDA has: (1) Received a recommendation from a device classification panel (an FDA advisory committee); (2) 'published the panel's recommendation for comment, along with a proposed regulation classifying the device; and (3) published a final regulation classifying the device. FDA has classified most preamendments devices under these procedures.

Devices that were not in commercial distribution prior to May 28, 1976, generally referred to as postamendments devices, are classified automatically by statute (section 513(f) of the act) into class III without any FDA rulemaking process. Those devices remain in class III and require premarket approval, unless and until the device is reclassified into class I or II or FDA issues an order finding the device to be substantially equivalent, under section 513(i) of the act, to a predicate device that does not require premarket approval. The agency determines whether new

devices are substantially equivalent to previously offered devices by means of premarket notification procedures in section 510(k) of the act (21 U.S.C. 360(k)) and part 807 (21 CFR part 807).

A preamendments device that has been classified into class III may be marketed, by means of premarket notification procedures, without submission of a premarket approval application (PMA) until FDA issues a final regulation under section 515(b) of the act (21 U.S.C. 360e(b)) requiring premarket approval.

Reclassification of classified postamendments devices is governed by section 513(f)(3) of the act. This section allows FDA to initiate reclassification of a postamendments class III device under section 513(f)(l) of the act, or the manufacturer or importer of a device to petition the Secretary of the Department of Health and Human Services for the issuance of an, order classifying the device in class I or class II. FDA's, regulations in § 860.134 (21 CFR 860.134) set forth the procedures for the filing and review of a petition for reclassification of such class III devices. To change the classification of the device, it is necessary that the proposed new class have sufficient regulatory controls to provide reasonable assurance of the safety and effectiveness of the device for its intended use.

II. Regulatory History of the Device

Cyclosporine assays are used for the quantitative determination of cyclosporine concentrations as an aid in the management of transplant patients receiving cyclosporine. Tacrolimus assays are used for the quantitative determination of tacrolimus concentrations as an aid in the management of transplant patients receiving tacrolimus. These assays are postamendments devices classified into class III under section 513(f)(l) of the act, and cannot, therefore, be placed in commercial distribution unless they are reclassified under section 513(f)(3) of the act or are the subject of an approved PMA under section 5 15 of, the act.

In accordance with section 513(f)(3) of the act and § 860.134, petitions were submitted by Dade Behring, Inc., on January 29, 2001, and by the Devices & Diagnostics Consulting Group,

Inc. (on behalf of Microgenics, Inc.), on April 4, 2001, requesting reclassification of cyclosporine assays from class III to class II. On its own initiative, the agency is including tacrolimus assays, in addition to cyclosporine assays, in the proposed reclassification. Cyclosporine and tacrolimus are both calcineurin inhibitors. Tacrolimup assays have a similar intended use, as an aid in the management of transplant patients, as well as similar technological and performance characteristics to cyclosporine assays. The agency believes it is taking a least burdensome approach by including tacrolimus assays in the proposed reclassification.

III. Device Description

Cyclosporine test systems are intended for the quantitative determination of cyclosporine concentrations as an aid in the management of transplant patients receiving cyclosporine. Tacrolimus test systems are intended for the quantitative determination of tacrolimus concentrations as an aid in the management of transplant patients receiving tacrolimus. Currently marketed cyclosporine and tacrolimus immunoassay test systems utilize monoclonal antibodies in order to enhance specificity of the assay for parent drug compound. FDA has also approved test systems based on chromatographic methods. Cyclosporine and tacrolimus test systems are typically used on automated laboratory analyzers. Whole blood is the matrix recommended for currently marketed test systems for cyclosporine and tacrolimus since these drugs are rapidly distributed into red blood cells and can be most reliably measured in this matrix.

IV. Proposed Reclassification

The agency is proposing to reclassify cyclosporine and tacrolimus test systems from class III to class II and has developed a guidance document which, when final, will serve as the special control. Elsewhere in this issue of the Federal Register, FDA is announcing the availability of this draft guidance for comment in accordance with FDA's good guidance practices (GGPs) regulation (21 CFR 10.115). We have determined that there is adequate valid scientific evidence in the public domain to support this reclassification action and, therefore, it was unnecessary to

refer the petitions to a classification panel for its review and recommendation. However, the agency did consult with certain Clinical Chemistry and Clinical Toxicology Devices panel members by mail regarding our revision of an existing 1993 guidance on cyclosporine and its adequacy as a special control for both cyclosporine and tacrolimus assays should the agency reclassify the cyclosporine and tacrolimus assays from class III to class II.

V. Risks to Health

After considering the information in the petitions, including the published literature, FDA's own experience and knowledge with cyclosporine and tacrolimus assays, and the medical device reports (MDRs) filed on cyclosporine and tacrolimus assays, FDA has. identified improper patient management as the only risk to health associated with these devices. Failure of the test to perform as indicated or error in, interpretation of result may lead to improper patient management in one of three ways. First, a falsely low cyclosporine or tacrolimus measurement could contribute to a decision to raise the dose above that which is necessary for therapeutic benefit. This could result in increased risk of toxicity from an elevated drug level. Second, a falsely high cyclosporine or tacrolimus measurement could contribute to a decision to decrease the dose below that which is necessary for immunosuppression. This could result in increased risk of rejection of the transplanted organ. Third, no firm therapeutic range exists for cyclosporine or tacrolimus concentrations. Optimal concentration ranges for a patient depend upon many factors such as transplant type, sensitivity of patient, coadministered drugs, time post-transplant as well as metabolite cross-reactivity of the specific commercial assay used, age, and other patient conditions. Therefore, use of assay results to adjust a treatment regimen without considering other clinical factors, could result in improper patient management.

VI. Special Controls

In addition to general controls, FDA believes that the draft guidance entitled "Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Draft Guidance for Industry

and FDA" is an adequate special control to address the risk to health described above. The class II special controls guidance provides information on how to meet premarket (510(k)) submission requirements for the assays in sections that discuss performance characteristics and labeling. The performance characteristics section describes studies integral to demonstration of appropriate performance and control against assays that may fail to perform to current standards. The labeling section addresses factors such as specimen requirements, assay procedure, quality control, limitations, therapeutic ranges, and performance characteristics. Because no firm therapeutic range exists for cyclosporine or tacrolimus concentrations, labeling for the assay includes a discussion of additional clinical considerations involved in interpretation of assay results essential for proper patient management. In this way, the cyclosporine and tacrolimus assays can be used as an aid in establishing a treatment regimen for individual patients. FDA tentatively believes that complying with the act and special control guidance document will provide reasonable assurance of the safety and effectiveness of these devices and adequately address the risk to health identified in section V of this document.

VII. FDA's Tentative Findings

The clinical efficacy of cyclosporine has been well-established over the past two decades. Monitoring of cyclosporine levels in blood plays a key role in patient management because of unpredictable pharmacokinetics, variable absorption, distribution, elimination and narrow therapeutic index unique to each patient (Ref. 1).

FDA has considered issues that could potentially complicate use or interpretation of cyclosporine assay results. One issue is, that no firm therapeutic ranges have been established (Ref. 2). While some patients may show signs of cyclosporine toxicity even with blood levels in the recommended therapeutic range, others, may show signs of inadequate immunosuppression within that same therapeutic range. The guidance document therefore recommends cautionary labeling and explanation for the user concerning therapeutic ranges.

Another issue is that the various immunoassays available differ in their accuracy and specificity for measurement of the parent cyclosporine compound (Refs. 3, 4, and 5). Average differences between two methods can be as high as 57 percent. In general, there is a positive bias of immunoassays compared with high performance liquid chromatography (HPLC) methods, as a result of metabolite cross-reactivity. HPLC methods are currently the only methods considered to be capable of measuring specifically parent compound. The biases observed are not constant and can vary, depending on factors such as transplant type and time post-transplant (Ref. 6). In addition, inter-individual differences, which can exceed the influence of the organ transplanted or hepatic function, have been observed (Ref. 3). Therefore, assay bias cannot be predicted for individual samples. Variability is less well-documented for samples collected in the early period after cyclosporine dosing, although some results indicate metabolite interference is less significant for these types of samples (Ref. 7). In light of the wide variability in cyclosporine assays, the guidance document recommends comparison of new test systems to a candidate reference HPLC method.

FDA believes clinicians are familiar with the need. to tailor an individual patient's dose based on overall allograft function along with any clinical signs of toxicity, in conjunction with the blood level. That is, the calcineurin inhibitor blood level is one measure that could be used as an adjunct to the care of transplant patients. Physicians managing the care of transplant patients also have resources for advice on the use of cyclosporine blood levels, and appropriate target ranges for blood levels in the early post-transplant (induction) stage as well as in the maintenance stage. These resources include the American Society of Transplantation, registries such as the North American Pediatric Renal Transplant Cooperative Study, and literature on the use and potential toxicities of this agent. FDA believes that these resources, in conjunction with appropriate labeling of the device, will sufficiently address the risks discussed above.

In conjunction with the downclassification of cyclosporine tests, FDA proposes to include tacrolimus test systems. Tacrolimus was first cleared for clinical use in 1994, and like cyclosporine,

is a calcineurin inhibitor. The immunosuppressive properties and molecular mechanisms of the two drugs are very similar (Ref. 8). Likewise, the toxicity profiles are very similar, although not identical. Tacrolimus raises the same issues as cyclosporine, related to the need for individual tailoring of dosing that is not solely dependent on blood drug levels. Similar issues to those discussed above also exist with regard to immunoassays for tacrolimus showing a positive bias compared with HPLC methods. FDA expects that the approach to validating analytical performance for test systems for these two drugs should be similar, as outlined in the draft guidance document.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.34(b) that this reclassification action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612) (as amended by subtitle D of the Small Business Regulatory Fairness Act of 1996 (Public Law 104–121), and the Unfunded Mandates Reform Act of 1995 (Public Law 104–4)). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maxirnize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive order. In addition, the reclassification action is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Reclassification of the device from class III to class II will relieve manufacturers of the cost of complying with the premarket approval

requirements in section 515 of the act. Because reclassification will reduce regulatory costs with respect to this device, it will impose no significant economic impact on any small entities, and it may permit small potential competitors to enter the marketplace by lowering their costs. The agency therefore certifies that this proposed rule, if finalized, will not have a significant economic impact on a substantial number of small entities. In addition, this reclassification action will not impose costs of $100 million or more on either the private sector or State, local, and tribal governments in the aggregate, and therefore a summary statement of analysis under section 202(a) of the Unfunded Mandates Reform Act of 1995 is not required.

X. Paperwork Reduction Act of 1995

FDA concludes that this proposed rule contains no new collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

XI. Request for Comments and Proposed Dates

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this proposed *rule* by *[insert date 60 days after date of publication in the* **Federal Register].** Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. FDA proposes that any final regulation that may issue based on this proposal become effective 30 days after its date of publication in the **Federal Register.**

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Shaw, L. M. et al., "Current Opinions on Therapeutic Drug Monitoring of Immunosuppressive Drugs," *Clinical Therapeutics,* 21:1632–1652, **1999.**

2. Oellerich, M. et al., "Therapeutic Drug Monitoring of Cyclosporine and Tacrolimus," *Clinical Biochemistry, 3* 1:309–3 16, 1998.

3. Steimer, W., "Performance and Specificity of Monoclonal Immunoassays for Cyclosporine Monitoring: How Specific Is Specific?," *Clinical Chemistry,* 45:371–381, **1999.**

4. Schutz, E. et al., "Cyclosporin Whole Blood Immunoassays (AxSYM, CEDIA, and EMIT): A Critical Overview of Performance Characteristics and Comparison With HPLC," *Clinical Chemistry,* 44:2158–2164, 1998.

5. Holt, D. W. et al., "New Approaches to Cyclosporine Monitoring Raise Further Concerns About Analytical Techniques," *Clinical Chemistry,* 46:872–874, *2000.*

6'. Hamwi, A. et al., "Cyclosporine Metabolism in Patients After Kidney, Bone Marrow, Heart-Lung, and Liver Transplantation in the Early and Late Posttransplant Periods," *American Journal of Clinical Pathology,* 114:536–543, 2000.

7. Femandez-Marmiesse, A. et al., "Comparison of Predose vs 2-h Postdose Blood Metabolites/ Cyclosporine Ratios in Kidney and Liver Transplant Patients," *Clinical Biochemistry,* 33:383–386, 2000.

8. Halloran, P. F., "Molecular Mechanisms of New Immunosuppressants," *Clinical Transplantation,* 10:118–123, **1996.**

9.' Braun, F. et al., "Clinical Relevance of Monitoring Tacrolimus: Comparison of Microparticle Enzyme Immunoassay, Enzyme-Lined Immunosorbent Assay and Liquid Chromatography Mass Spectrometry in Renal Transplant Recipients Converted From Cyclosporine to Tacrolimus," *Transplantation Proceedings,* 28:3175–3176, 1996.

10. Jusko, W. J. et al., "Consensus Document: Therapeutic Monitoring of Tacrolimus (FK–506)," *Therapeutic Drug Monitoring,* 17:606–614, **1995.**

List of Subjects in 21 CFR Part 862

Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 862 be amended in subpart B as follows:

PART 862-CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES

1. The authority citation for 21 CFR part 862 continues to read as follows:

Authority: 21 U.S.C. 351, 360, 360c, 360e, 360j, 371.

2. Section 862.1235 is added to subpart B to read as follows:

§ 862.1235 Cyclosporine test system.

(a) *Identification.* A cyclosporine test system is a device intended to quantitatively determine cyclosporine concentrations as an aid in the management of transplant patients receiving therapy with this drug. This generic type of device includes immunoassays and chromatographic assays for cyclosporine.

(b) *Classification.* Class II (special controls). The special control is "Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA."

3. Section 862.1678 is added **to** subpart B to read as follows:

§ 862.1678 Tacrolimus test system.

(a) *Identification.* A tacrolimus test system is a device intended to quantitatively determine tacrolimus concentrations as an aid in the management of transplant patients receiving therapy with this drug. This generic type of device includes immunoassays and chromatographic assays for tacrolimus.

(b) *Classification.* Class II (special controls). The special control is "Class II Special Controls Guidance Document: Cyclosporine and Tacrolimus Assays; Guidance for Industry and FDA."

Dated: 2/11/02

February 11, 2002.

Linda S. Kahan

Linda S. Kahan,
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